Macromolecular thermodynamics and its possible relevance in physiology

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Scientific Note

Macromolecular thermodynamics and its possible relevance in physiology

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1. Introduction

The purpose of this paper is to call attention to a newly discovered diffusional process which could be of importance in understanding the physiological processes involving the transport of macromolecules or of any species associated with transporting macromolecules. Maerker (1973) and Desremaux *et al* (1971) have discovered that macromolecules dissolved in a flowing fluid may be concentrated by the flow process in heterogeneous porous media. A further detailed experimental verification of this phenomenon has been described by Dominguez and Willhite (1977). It appears that the concentration changes depend upon the type of macromolecules involved and the flow rate in the main stream of the moving fluids. A thermodynamic analysis of the Chauveteau–Maerker effect has been published by Metzner (1977). This analysis depends upon the observation that in a moving, deforming fluid dissolved macromolecules will become aligned and stretched, thus changing their entropy and free energy levels. In any flow process in which the stress or strain rate levels vary with position within the fluid, the molecular orientation and extension, and consequently the free energy, will also vary with position. In order for the free energy, at steady state, to become independent of position, compensating concentration gradients will be induced. The net result of these processes will be to cause the macromolecules to diffuse toward regions of low stress level—toward any 'deadwater' regions behind obstructions or in fenestra. Independently, Terrill and Malone (1977) applied similar considerations to the identification of radial concentration gradients within the flowing stream itself.

2. Theory

To illustrate how the Chauveteau–Maerker effect with its flow-induced concentration differences may relate to physiology, let us consider the structure of the endothelial layers in a typical arterial wall. Three kinds of structures, which, for our purposes may be considered to be cavities within the wall of the endothelium can be distinguished (Majno and Joris (1978), Middleman (1972), Weinbaum and Caro (1976)): intercellular channels, void spaces and the cavioles which are precursors to vesicules (figure 1). As the arterial bloodstream flows past any of these structures, macromolecular species in the flowing stream will diffuse into these wall cavities; the experimental

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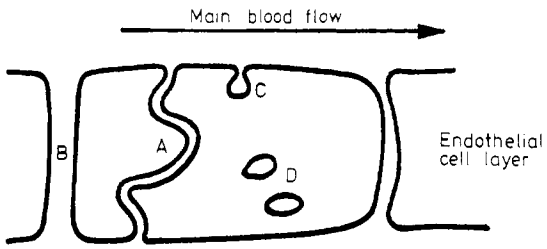

Figure 1. Endothelial wall with cavities: A: intercellular channels; B: void spaces; C: cavioles; D: vesicules.

results of Maerker and of Dominguez and Willhite show that the concentration levels in these cavities may exceed those in the mainstream by an appreciable margin. The subsequent uptake of these species into the remainder of the intima will, of course, be dependent on the concentration levels within these cavities. Additionally, the possible existence of 'backwater' stagnant zones in the valleys between the endothelial folds has been suggested by Chisolm *et al* (1972); these would likewise produce stagnant or semistagnant fluid regions of high concentration.

At thermodynamic equilibrium between the flowing fluid and that located in a wall cavity or stagnant fluid region the concentrations of macromolecular species in the two regions are related by (Metzner 1977)

$$c_{wc}/c_s = \exp(\text{tr } \mathbf{P}/2c_s RT). \tag{1}$$

Here c_{wc} denotes the concentration of a given macromolecular species in the wall cavity or in a stagnant backwater region; c_s denotes the concentration of the same species in the adjacent flowing stream; R and T are the universal gas constant and the absolute temperature. The term tr $\mathbf{P}$ denotes the trace of the stress tensor and is a measure of the stretch of the macromolecules in the flowing stream. It is this term which gives rise to an entropy difference between macromolecules in the flowing and deforming fluid and those in any adjacent stagnant fluid in which the macromolecules would assume their more or less random coil configuration (figure 2).

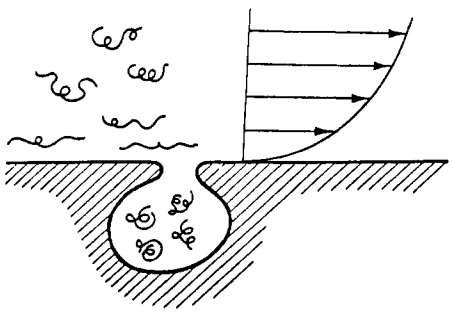

Figure 2. Stretched and coiled molecules in the endothelial system.

If the blood rheology is described by a Maxwell–Oldroyd constitutive equation (Janssen and Janssen-van Rosmalen (1978), White and Metzner (1963)) the term tr $\mathbf{P}$ is given by

$$\text{tr } \mathbf{P} = 2\mu\theta\Gamma^2 \tag{2}$$

in which μ denotes the viscosity of the blood at the shearing rate Γ and θ is the

viscoelastic time constant contributed by the macromolecular species in question. Combining equations (1) and (2) and linearising the exponential (an operation expected to be valid for the modest concentration changes likely in physiological systems) gives:

$$c_{wc} = c_s + (\mu\theta\Gamma^2/RT). \tag{3}$$

The use of this equation is particularly convenient since the viscosity (μ) and the viscoelastic time constant (θ) are directly measurable standard quantities.

This equation states that the macromolecular species in question will be present in wall cavities at concentration levels exceeding those in the flowing stream by an amount depending on the rheological properties of the fluid (μ, θ) and the square of the local shear rate Γ. This predicted concentration excess will presumably influence the diffusional transport of these molecular species from the wall cavities into other parts of the endothelium, including the cells themselves. In fact, in the case of synthetic polymer solutions for which data are available, the second term on the right-hand side of equation (3) may be appreciably larger than the first. Speculatively, it is attractive to attribute the origin of the free cholesterol ester and of the cholesterol monohydrate in atherosclerotic plaque to such concentration excesses, but there is no firm basis for doing so at present. Nevertheless, Carew (1971) and Fry (1973) report that in *in vitro* experiments the uptake of albumin by the artherial wall at higher stress ranges varies with the square of the shear stress (or shear rate). This identity of the dependence as predicted by equation (3) and found experimentally is very striking.

In order for equation (3) to be related to the physiological transport, at least some of the macromolecular species involved must be capable of deformation, stretching or alignment in the flowing bloodstream, thus giving rise to a viscoelastic response (θ). Deformation of lipoproteins by shearing forces, although mentioned (Moacanin *et al* 1970), has evidently not been measured directly. The viscoelastic properties of blood, although normally too small to measure under steady state conditions (Copley and King (1975)), have, however, been measured in unsteady state experiments, (Chien *et al* (1975)) and appear to be of sufficient magnitude for the last term of equation (3) to be significant. Additionally, the presence of fibrinogen has been shown to be closely linked to the viscoelastic properties of the blood (Merril *et al* (1969)). The polymerisation of fibrin in a shear field has recently been reported by Clark (1978) and is very similar to the entropy-induced crystallisation of synthetic polymers reported by Zwijnenburg and Pennings (1975, 1976), McHugh (1975) and by Janssen and Janssen-van Rosmalen (1978). Thus the migration of some of the macromolecular components of blood towards 'backwater' regions may be expected, and fibrinogen will be one of the species involved in this process. Since we are dealing with very slow processes in physiology and possibly with some species having limited solubility, even a minor concentration excess (equation 3) may be quite significant.

At the intima on arterial flow dividers, where the stress levels may be very high, however, the diffusion is not expected to be significant. Equation (3) is an equilibrium relationship. Flow for a period of the magnitude of the fluid relaxation time θ is required for the macromolecular stretch, which is the basis of equation (1), to occur. Thus, a fluid element having velocity v will be transported downstream a distance $v\theta$ before the entropy changes and hence the concentration changes predicted will occur fully. In other words, because of the memory effects in the fluid (expressed in the time constant θ) in a velocity field in which the hydrodynamic stress levels vary strongly with position, we would expect maximum concentration differences to occur slightly downstream from the position of the maximum stress level.

3. Concluding comments

This paper presents a hypothesis for the diffusion of macromolecules which has the following characteristics. It indicates that diffusion should occur under conditions of high haemodynamic stress or shear rate, that the subsequent concentration differences should vary quadratically with shear rate in steady flow and that a region of length $v\theta$ downstream from a flow divider will be relatively unaffected. This mechanism focuses attention on the possibly important role of fibrinogen and of other macromolecular species which can undergo large extensions in the shear field.

To review, the underlying physical basis of the concentration differences predicted by equation (3) is in the possibility of stretching the species by fluid shear. In the absence of any such stretch the last term of equation (3) would be zero and the concentration in a wall cavity would be identical to that in the bulk of the fluid. Reference to Maerker (1975), Desremaux *et al* (1971), Dominguez and Willhite (1977) and Metzner (1977) will show that the predicted concentration differences are inferred from macroscopic measurements of the retention of macromolecules in porous media of complex internal geometry. Direct measurements with synthetic polymers (Metzner *et al* 1978, Rangel-Nafaile 1979) give significant concentration changes of the order of magnitude predicted by equation (3). Until this is established more precisely, however, equations (1) and (3) should be viewed as being generally indicative rather than as precise, quantitatively verified predictions.

The concentration changes given by these relations are believed to apply generally to all inhomogeneous flows of viscoelastic fluids, i.e. to all flows of these fluids in which there is a stress gradient. As such they may influence diffusional processes rather generally in physiological systems.

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